

# PATENT COOPERATION TREATY

From the Japan Patent Office

(INTERNATIONAL SEARCHING AUTHORITY)

# PCT

To: Agent of Applicant  
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## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43-2.1)

|                                                                                                                      |                                                          |                                               |  |
|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------|--|
|                                                                                                                      |                                                          | Date of mailing<br>(day/month/year) 01.6.2004 |  |
| Applicant's or agent's file reference 09624                                                                          |                                                          | For Further Action<br>see paragraph 2 below   |  |
| International application No.<br>PCT/JP2004/004612                                                                   | International filing date (day/month/year)<br>31.03.2004 | Priority date (day/month/year)<br>15.04.2003  |  |
| International Patent Classification (IPC) Int. Cl. <sup>7</sup> C12N5/06, C12N5/10, C12N15/09, A61K48/00, A01K67/027 |                                                          |                                               |  |
| Applicant<br>Shirankai Kyoto University Faculty of Medicine Alumni Association Inc.                                  |                                                          |                                               |  |

1. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43-2.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. Further Action

If a demand for international preliminary examination is made, this written opinion is the first drawn up by the International Preliminary Examining Authority (IPEA) except that this does not apply where the Applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Established this written opinion  
17.05.2004

|                                                                                                                           |                                                                                                                                                                                                                                                                                                           |                                                  |         |                                           |  |
|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------|-------------------------------------------|--|
| Name and mailing address<br>Japan Patent Office (ISA/JP)<br>4-3, Kasumigaseki 3-chome<br>Chiyoda-ku, Tokyo 100-8915 Japan | <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;">Authorized officer<br/>Examiner<br/>Akiteru Tamura</td> <td style="width: 30%; text-align: center;">4N 8412</td> </tr> <tr> <td colspan="2">Telephone No. 03-3581-1101 extension 3448</td> </tr> </table> | Authorized officer<br>Examiner<br>Akiteru Tamura | 4N 8412 | Telephone No. 03-3581-1101 extension 3448 |  |
| Authorized officer<br>Examiner<br>Akiteru Tamura                                                                          | 4N 8412                                                                                                                                                                                                                                                                                                   |                                                  |         |                                           |  |
| Telephone No. 03-3581-1101 extension 3448                                                                                 |                                                                                                                                                                                                                                                                                                           |                                                  |         |                                           |  |

**WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY**

Intern. application No.PCT/JP2004/004612

**I. Basis of the opinion**

1. Unless otherwise indicated under this item, this written opinion was drawn up based on the language in which the international application was filed.  
[ ] This written opinion is in the following language \_\_\_\_\_ which is:  
The language of a translation furnished for the purposes of the international search (under Rule 12.3 and 23.1 (b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of
  - a. type of material
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material
    - ☐ on paper
    - ☐ in electronic form
  - c. time of filing/furnishing
    - ☐ contained in the international application in written form
    - ☐ filed together with the international application in computer readable form
    - ☐ furnished subsequently to this Authority for the purposes of search
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY**

Intern. application No. PCT/JP2004/004612

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,  
☒ claims No. 18

because:

- ☒ the said international application, or the said claim No. 18 relate to the following subject matter which does not require an international preliminary examination (specify):

The claim is described the invention relating to a treatment method for human.

- ☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- ☐ the claims or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for the said claims No. 18

- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C (guideline for preparing specification etc containing base sequence and/or amino acid sequence) of the Administrative Instructions In that:

the written form

- ☐ has not been furnished  
☐ does not comply with the standard

the computer readable form

- ☐ has not been furnished  
☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☐ have not been furnished  
☐ do not comply with the technical requirements

- ☐ See separate sheet for further details.

WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY

Intern. application No.PCT/JP2004/004612

V. Reasoned statement under Rule 43-2.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

|                               |        |                           |     |
|-------------------------------|--------|---------------------------|-----|
| Novelty (N)                   | Claims | <u>1-11, 14-16, 19-27</u> | YES |
|                               | Claims | <u>12, 13, 17</u>         | NO  |
| Inventive Step (IS)           | Claims | _____                     | YES |
|                               | Claims | <u>1-17, 19-27</u>        | NO  |
| Industrial Applicability (IA) | Claims | <u>1-17, 19-27</u>        | YES |
|                               | Claims | _____                     | NO  |

2. Citations and Explanations

- Reference 1: Life Science Foundation (annual report), Heisei 14 edition (01 March, 2003) pp.17-19
- Reference 2: Cell.Mol.Life Sci., Vol.58, No.8, pp.1061-1066 (2001)
- Reference 3: Science, Vol.287, No.5457, pp.1489-1493 (2000)
- Reference 4: Gendai Kagaku Zokan 41, Saisei Igaku·Saisei Iryo (01 July, 2002) pp.24-28
- Reference 5: Proc.Natl.Acad.Sci.USA, Vol.98, No.23, pp.13090-13095 (2001)
- Reference 6: FEBS Lett., Vol.475, No.1, pp.7-10 (2000)

Claims 1-16

The invention described in claims 1-16 lacks an inventive step over References 1-3.

Reference 1 describes that even when using the cell differentiation suppressive factor LIF in the cultivation and maintenance of ES cells, it is troublesome to maintain an undifferentiated state while retaining the capacity of multiple differentiation, and that an investigation using the seminiferous tubule transplantation method has been ongoing to determine whether spermatogonia maintained and proliferated with the addition of GDNF (glial cell-derived neurotrophic factor) possesses the function for stem cells.

Reference 2 describes that GDNF and LIF, a member of the IL-6 family, control the self-proliferation and differentiation of stem cells in spermatogenesis.

Reference 3 describes that GDNF controls the self-proliferation and differentiation of undifferentiated spermatogonia, including spermatogonial stem cells.

Here, for the culture of stem cells, use of feeder cells and addition of growth factors such as EGF, bFGF etc. are usually performed.

Supplementary column

Continued from column V

Claims 12, 13 and 17

The invention described in claims 12, 13 and 17 lacks novelty over Reference 4 cited in the International Search Report.

Reference 4 describes that the spermatogenic capacity was acquired by transplanting spermatogonial stem cells to the testis.

Claims 17 and 19-23

The invention described in claims 17 and 19-23 lacks an inventive step over References 1-4 cited in the International Search Report.

Implanting spermatogonial stem cells maintained and grown using GDNF and LIF into non-human cells to obtain sperm, embryo or non-human offspring can be easily done by those of ordinary skill in the art by a conventional means according to the teachings of References 1-4.

Claims 24-27

The invention described in claims 24-27 lacks an inventive step over References 1-6 cited in the International Search Report.

References 5 and 6 describe a method of producing a transgenic mouse by introducing an exogenous gene to spermatogonial stem cells using a retrovirus.